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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,050	06/29/2007	Kazuya Hosokawa	JCLA21671	3526
23900	7590	12/08/2011	EXAMINER	
J C PATENTS 4 VENTURE, SUITE 250 IRVINE, CA 92618			TSAY, MARSHA M	
			ART UNIT	PAPER NUMBER
			1656	
			MAIL DATE	DELIVERY MODE
			12/08/2011 PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

**Application No.**

10/599,050

**Applicant(s)**

HOSOKAWA ET AL.

**Examiner**

Marsha Tsay

**Art Unit**

1656

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 23 November 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.  
 NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 1-4, 11-18, 20, 38, 39, 42, 43, 45-48, 50 and 58-60

Claim(s) withdrawn from consideration: 5, 21-36, 40, 41, 44, 49 and 51-57

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_

13. ☐ Other: \_\_\_\_\_

/Marsha Tsay/  
Patent Examiner, Art Unit 1656

Continuation of 5. Applicant's reply has overcome the following rejection(s): the rejection of claims 58-60 under 35 U.S.C. 112, second paragraph.

Continuation of 11. does NOT place the application in condition for allowance because: the reasons for maintaining the 103(a) rejections are the same as previously noted in the Office action of September 8, 2011. However, Applicants' after final remarks of November 23, 2011, will be briefly addressed herein.

Regarding Applicants' remarks on the Wells et al. reference, it should be noted that the Wells et al. reference was cited as evidence to show that it was known in the art at the time the invention was made that additive mutagenesis is a tool used in designing functional properties in proteins, in general. It was not cited to note only subtilisin. One of ordinary skill would know that subtilisin was the protein model used to demonstrate additive mutagenesis. Applicants are reminded that "the references cannot be used in isolation, but for what they teach in combination with the prior art as a whole. In re Merck, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

Regarding Applicants' remarks that it was never easy to find specific effective combinations. For example, H43M disclosed in Arcone et al. still maintain thrombin activity, but 205A or G203A did not show detectable activity (table 1). Accordingly, in view of Arcone and Well, one of ordinary skill would have selected the combination of positions 205 and 203, rather than 43 and 205.

It should be noted that "a prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention." See W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). In this instance, Arcone et al. disclose that H43N dramatically impaired the enzyme activity as well (p. 173). Further, one of ordinary skill would reasonably select the combination of 43 and 205 since both 43 and 205 are identified as residues in the catalytic triad.

Regarding Applicants' remarks that the effect of the claims of the instant invention is unexpected and non-obvious, it should be noted that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 441 F.3d 977,987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). In this instance, single amino acid substitutions in the catalytic triad were identified to disrupt enzyme activity, it would be reasonable for one of ordinary skill to combine the single amino acid substitutions selected from H43, D99 and S205, in order to arrive at the combination of H43 and S205 because there are only three residues at the catalytic triad and it would be reasonable to determine which two residues, when substituted in combination, will make a modified thrombin protein that has approximately no enzymatic activity, using the technology of Morrison et al. and Wells et al.

See also the Office action of September 8, 2011.

For at least these reasons, the claims remain rejected under 35 U.S.C. 103(a).